Negative scotopic ERG and photopic ERG ON response impairment in a patient with normal dark adaptation

Subtitle: Negative ERG with normal dark adaptation

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Abstract

Purpose: To present ocular findings in a patient who showed negative scotopic electroretinogram (ERG) and reduced ON response, but normal dark adaptation.

Case: A 18-year-old Japanese male patient who complained of severe asthenopia. His corrected visual acuities were 1.2 in both eyes. His fundi were normal. He had normal contrast sensitivity and normal dark adaptation.

Methods: The patients underwent ERG (including the standard protocol and photopic long flash recordings).

Results: The amplitudes of the rod ERG b-wave were reduced. The scotopic standard combined ERG response showed negative configuration. The photopic response to long flash revealed the reduced b-wave (ON response), while the amplitude of the first peak of the d-wave (OFF response) was within the normal range.

Conclusions: Postsynaptic abnormalities in both the rod and cone ON-pathways, which are often found in patients with night blindness, were suggested in the ERG findings, but the dark adaptation of our patient was normal. Neuromuscular evaluation of the patient and ophthalmological evaluation,

including ERG, of his parents were normal. To our knowledge, the ophthalmological and electrophysiological findings of our patient cannot be attributed to any known clinical entity.

Introduction

A negative scotopic electroretinogram (ERG), i.e., selective reduction in amplitude of the b-wave such that it does not exceed that of the a-wave [1], can be observed often in diseases with reduced photopic ON response dysfunction and minimal or no fundus abnormality. These disorders include two groups in terms of night blindness: complete and incomplete congenital stationary night blindness (CSNB) [2, 3], melanoma associated retinopathy (MAR) [4, 5], and acquired unilateral night blindness [6], which are all characterized by varying degrees of night blindness, and, on the other hand, dystrophinopathy [7, 8], and autosomal dominant negative ERG (ADNE) [9], which have normal dark adaptation.

Here we report a Japanese male patient with a negative ERG, reduced ON response, and normal dark adaptation. However, no abnormal findings could be found on muscle evaluation and the ophthalmological and ERG evaluation of his parents. Koh et al [10] reported that, for some of the patients who showed negative scotopic ERG with or without reduced photopic ON response, a definitive diagnosis could not be established. They described that some of these patients with negative scotopic ERG for whom a definitive diagnosis was not possible had a number of potential diagnosis, e.g., macular dysfunction, a history of retinal detachment surgery, a long history of heavy

alcohol and tobacco use, a history of ischemic heart disease, or cerebrovascular disease. Our patient underwent not only full ophthalmological examinations but also detailed systemic examinations; however, he showed no abnormality except for the ERG findings and he had an otherwise unremarkable ophthalmological and systemic history. To our knowledge, the ophthalmological disorder of our patient cannot be assigned to any clinical entity.

Patient

An 18-year-old Japanese man came to our university eye clinic. He complained of severe asthenopia present since he was 17 years old. He denied use of medications or drugs. There was no parental consanguinity in his family, and no family history of night blindness, inherited eye disease, amblyopia, nystagmus or muscle disease. The corrected visual acuity was 1.2 for each eye, with optical correction (-6.75-2.75 axis 180, right eye; -6.75-2.50 axis 180, left eye). The extraocular muscle function was normal and no nystagmus was evident. The size of the pupil in both conditions of dark and light, light reflex, and the near response of the pupil showed no abnormality. The cornea, lens, and vitreous were clear. No abnormal finding was observed on ophthalmoscopy or by fluorescein angiography. Goldmann kinetic perimetry and automated

static perimetry (Humphrey, USA) showed no abnormal findings. Color vision was normal by testing with the Farnsworth D-15 panel, Ishihara pseudoisochromatic plates, and Nagel anomaloscope. Electro-oculogram showed normal light rise (the ratio of light peak and dark baseline was 2.1 in the right eye and 2.3 in the left). The dark adaptation curve, examined with the Goldmann-Weekers adaptometer (HAAG-STREIT AG, Koelnz/Bern, Switzerland), showed normal cone and rod thresholds and normal cone-rod break (Figure 1(a)). The contrast sensitivities measured by CTS-5000 (Cadwell, Kennewick, WA, USA) were normal in both eyes at seven points within the range of 0.78-12.4 cycle/degree of spatial frequency (the methods were described in the previous report [11]). He did not show any abnormalities on general physical and neurological examinations. Electromyography (EMG) and brain magnetic resonance imaging showed no abnormality. His asthenopia could not be reduced by means of glasses nor contact lenses.

Methods

ERG

The ERG procedure complied with the ISCEV standard protocol [12]. The methods were similar to those described in the previous reports [11, 13].

Both eyes were dilated with a mydriatic and subjects were dark-adapted

for at least 45 minutes before testing. The responses were obtained from Burian-Allen bipolar electrodes (Hansen Ophthalmic Instruments, Iowa City, IA, USA). The stimulus was a 10-μs-xenon flash (ERG Photic Stimulator, SLS-4100, Nihon Kohden, Tokyo, Japan) delivered by means of a Ganzfeld dome (Sanso, Tokyo, Japan). Stimulus intensity was controlled by means of neutral density filters (Fujifilm, Tokyo, Japan). Scotopic rod ERG and scotopic standard combined ERG were recorded with a 0.5 to 100 Hz filter setting. Oscillatory potentials (OPs) were recorded with a 50 to 500 Hz filter setting. The flash intensities were 0.13 cd·s/m^2 (0.7 log scot td-s) for the scotopic rod ERG, and 109.5 cd·s/m^2 (3.6 log scot td-s) for the scotopic standard combined ERG and OPs. The single flash cone ERG and 30-Hz flicker ERG were recorded under 30 cd/m^2 background illumination after at least 15 minutes of light adaptation. The flash intensity was 109.5 cd·s/m^2 (3.6 log scot td-s) for the single flash cone ERG. The light intensity of 1120 cd/m^2 was used for 30-Hz flicker ERG recording. Amplitudes and implicit times from the responses were calculated and compared with the values from 18 normal subjects aged 12-34 years (mean age: 22.6 years) (Table 1).

Cone "on" and "off" response recordings: The cone ON and OFF responses were recorded under 30 cd/m^2 background illumination after at least 15 minutes of light adaptation. White stimuli (200 msec duration) were presented every 2

sec (Electric stimulator, SEN-3201, Nihon Kohden, Tokyo, Japan) delivered by means of a Ganzfeld dome (Sanso, Tokyo, Japan). The long flash intensity was 1120 cd/m^2 (ERG full-field stimulator, IS-400A, Sanso, Tokyo, Japan). The responses were recorded with a 0.5 to 500 Hz filter setting. Thirty responses were summed and averaged. Amplitudes of the patient's a-, b-, and d-waves were calculated, and compared with the values from 18 normal subjects aged 12-34 years (mean age: 22.6 years) (Table 1)

Informed consent was obtained from the patient and normal subjects for each of the procedures after the explanation of the nature and possible consequences of the study.

Results

The ERGs were similar in both eyes. The ERG results from normal controls and from the right eye of the patient are summarized in Table 1.

Standard ERGs: The standard ERG responses from the right eye of the patient are shown in Figure 1(b). The amplitude of the rod ERG b-wave was reduced. In the scotopic standard combined ERG, the amplitude of a-wave was within the normal range, however, those of the b-waves were reduced. As a result, the b/a-wave amplitude ratios were reduced to 0.88. The amplitude of each OP (OP1, OP2, and OP3) was measured from a baseline drawn as a

first-order approximation between the troughs of successive wavelets. The amplitudes of OP1, OP2, and OP3 were larger than normal range, but the implicit times of OPs were within the normal range. The responses in the photopic single flash cone ERG and in the 30-Hz flicker ERG were normal.

----- Figure 1 near here -----

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Photopic ERGs to long flashes: The responses to long flashes in photopic condition from the right eye of the patient are shown in Figure 1(c). The long-duration flash shows a normal cone-generated a-wave followed by a reduced b-wave (ON response), and consequently the b/a-wave amplitude ratios were reduced to 0.71. In our settings, the response after the termination of a light stimulus (d-wave) is consisted of two large sharp positive peaks. We measured the amplitude of the first large positive peak as the amplitude of d-wave, because the first positive peak is always larger than the second positive peak in normal controls. The amplitude of the d-wave (OFF response) of this patient was within the normal range. The second positive peak was smaller than the first positive peak in normal subjects (solid arrow in Figure 1(c)), however, the second positive peak was approximately as large as the first one in this

patient (dashed arrow in Figure 1(c)), i.e., the second positive peak of this patient was relatively large.

Discussion

In our patient, the scotopic and photopic a-waves were normal, indicating normal function of the outer segments of rods and cones. It has been suggested that the scotopic ERG b-wave is the result of depolarization of ON-bipolar cells [14, 15]. Therefore, the reduced amplitudes of the b-wave in the rod ERG and in the scotopic standard combined ERG might result from a postsynaptic abnormality in the rod ON-pathway. The reduction in the photopic ON response could be explained by a postsynaptic abnormality in the cone ON-pathway, which generates this response [16, 17]. From the above results, a postsynaptic abnormality in both rod and cone ON-pathways probably contributes to the ERG changes of our patient.

ON-pathway is considered to influence the contrast sensitivity [18, 19]. Clinically, impairments of contrast sensitivity were reported in disorders with ON-pathway dysfunctions, such as MAR [20], complete CSNB [20], and our another patient which was reported previously [11]. Interestingly, this patient, who showed also the ON-pathway dysfunctions, revealed completely normal contrast sensitivities. It is not understood why the contrast sensitivities

are altered differently among disorders with ON-pathway dysfunctions, but presumably the ON-pathways might be impaired variously by different etiologies, thus the functions of not only contrast sensitivity but also dark adaptation are variable among the disorders.

The ERG phenotype of the patient described in this report, i.e., reduced photopic ON response and reduced b-wave of scotopic bright flash response, resembles complete CSNB [2], MAR [4], acquired unilateral night blindness [6], dystrophinopathy [7], and ADNE [9]. Among these disorders, the findings of dark adaptometry are useful for differential diagnosis [11]. Because the patient in this report did not show impairment of dark adaptation, he might be considered as having a possible dystrophinopathy [8] or ADNE [9]. Our patient was male, and he has no systemic problems and no abnormal findings in EMG; therefore, the ERG changes cannot be attributed to a dystrophinopathy. ADNE has been reported only in one family [9] in which a negative scotopic ERG, reduced rod b-wave, and photopic ON response impairment were detected in subjects from three generations in an autosomal dominant manner. They showed amblyopia and nystagmus only in childhood suggesting delayed visual development. Our patient and his parents had neither amblyopia nor nystagmus during their childhood. The corrected visual acuities were 1.2 in each eye of his father and his mother. They had normal fundi in both eyes.

Further, ERGs showed no sign of ON-pathway dysfunctions. Consequently, our patient's ERG abnormalities cannot be attributed to ADNE. In the report by Koh, Hogg, and Holder concerning the incidence of negative ERG [10], a definitive diagnosis could not be established for 25 out of 128 patients who showed negative ERG, and 40% of these patients demonstrated a selective abnormality in the photopic ON response. It is also described that some of the undiagnosed patients with negative scotopic ERG had a number of potential diagnosis [10] (see Introduction). Our patient showed no abnormality except for ERG findings; thus the possible cause of the abnormal ERG of the patient in this report could not be speculated.

The size of the d-wave in the photopic long flash ERG was not altered, but the configuration of the d-wave was changed in our patient, i.e., the second positive peak of our patient was as large as the first positive peak. Recently, details of the retinal origins of the d-wave in primates have been published [21]. The cone OFF-pathway as well as the responses of cone photoreceptors and the cone ON-pathway contribute to the configuration of the d-wave. The first positive peak reflects mainly the activity of the cone OFF-pathway. The second positive peak was composed of the activities of cone OFF-pathway, cone ON-pathway, and cone photoreceptors. Because cone ON- and OFF-pathways have opposite polarity against each other [21], theoretically,

the second positive peak of the d-wave could become enlarged when the activities of cone ON-pathway are diminished. In another patient with ON-pathway dysfunction whom we examined and reported previously [11], the second positive peak of the d-wave was also relatively large, when it was compared with that of normal controls.

Although the differences of the scotopic OPs between the normal subject and our patient are not apparent in the “Standard combined ERG recording setting” (the top row in Figure 1(b)), the scotopic OPs in the “Oscillatory potentials recording setting” of our patient were supernormal without delays (Table 1 and the bottom row in Figure 1(b)). Supernormal OPs could occur rarely [22-24]. The OPs in the genetically altered mice that lack $GABA_C$ receptors, which modulate inner retinal circuitry, were larger than those in the wild type mice [22], however, the amplitudes of a- and b-waves in the knock-out mice are not altered. In the condition which is related to the function of dopamine receptors, OPs are not only enhanced but also delayed, further, both a- and b-wave are mildly reduced [23]. In patients with CSNB, only OP2 is enhanced [24]. Therefore, the OP findings of our patient do not fit to those conditions.

There was the difference of the photopic second OPs before the peak of the b-wave between this patient and the patient who was reported previously

[11]. Both the first and the second photopic OPs are missing in patients with complete CSNB, which shows completely loss of photopic ON response, and only the second photopic OP is absent in patients with DMD, which retains some ON response [7]. This difference might be explained by the degree of impairments of photopic ON responses [7]. Although both patients showed similar ERG findings in the photopic ERG to long flashes (the photopic long flash b/a wave ratio was 0.63-0.64 in the patient [11], and 0.71 in this patient), the photopic second OP was reduced in the patient [11], but it was preserved in this patient. The photopic OP findings in our patient cannot be explained only by photopic ON responses.

Our patient's asthenopia could not be reduced by means of glasses or contact lenses. All of his visual functions, including visual acuity, visual field, color vision, and contrast sensitivity, were normal. Whether there is a relationship between his asthenopia and ON-pathway dysfunctions in our patient is still unclear. It cannot be assumed whether the patient has an acquired problem or a lifelong problem that only was appreciated on initial evaluation with the ERG.

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Legends to figure & table

Figure 1

(a) Dark adaptation curve measured with Goldmann-Weekers adaptometer. Shadow zone shows the normal range obtained from 12 normal control subjects. Closed circles; the right eye of the patient.

(b) Standard ERGs in a normal subject and those in the right eye of the patient.

(c) Photopic ERGs to long flash stimulation (200 msec) from a normal subject and those in the right eye of the patient. The b-wave (ON response) of the patient was reduced. There was no apparent difference of the first positive peak of the d-wave (OFF response). The second positive peak of the patient (dashed arrow) was relatively larger than that of the normal subjects (solid arrow), when they are compared with the first peaks.

Table 1. Electroretinogram results of the patient and normal controls. Asterisk (*) indicates the value outside the normal range.